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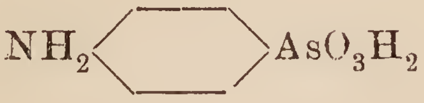
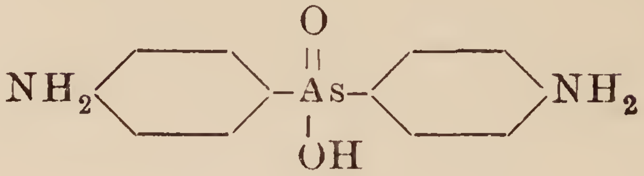
LXXXIII.—*Substituted Phenylarsinic Acids and their Reduction Products, and the Estimation of Arsenic in such Compounds.*

By Robert George Fargher.

In the preparation of *p*-aminophenylarsinic acid (I) by Béchamp's method (*Compt. rend.*, 1863, **56**, 1173), Pyman and Reynolds (T., 1908, **93**, 1180) isolated as a by-product a small proportion of bis-*p*-aminophenylarsinic acid (*pp*′-diaminodiphenylarsinic acid) (II).

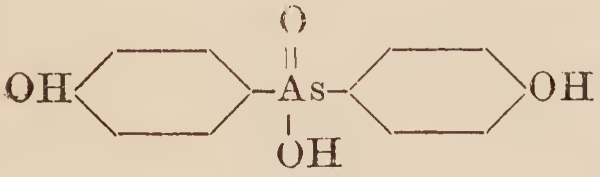


(I.)

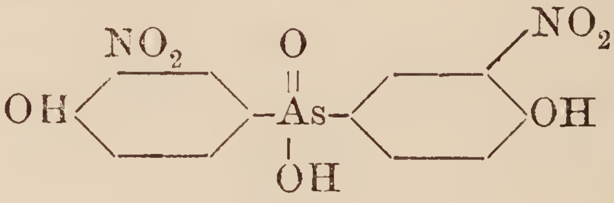


(II.)

In view of the close relation existing between the two acids and the importance of the former as the starting point for the preparation of salvarsan, it seemed to be of interest to prepare the corresponding 3 : 3′-*dinitro*-4 : 4′-*dihydroxydiphenylarsinic acid* (IV) and to examine its reduction products.

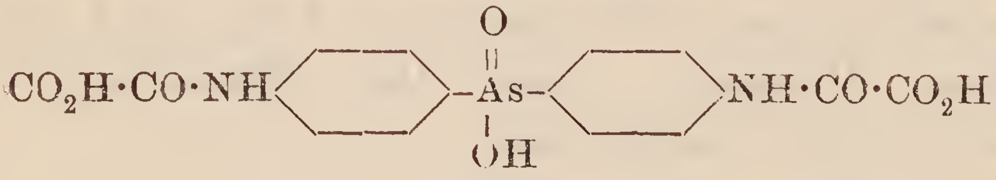


(III.)



(IV.)

For the preparation of this acid, the two methods described for 3-nitro-4-hydroxyphenylarsinic acid (Bertheim, *Ber.*, 1911, **44**, 3092; Benda and Bertheim, *loc. cit.*, 3445; Benda, *loc. cit.*, 3449) can be used. In the first, the amino-acid (II) is converted into the corresponding hydroxy-acid (III) (Benda, *Ber.*, 1908, **41**, 2371) and subsequently nitrated under suitable conditions. This method gives excellent results. In the second, the amino-acid is converted into its *oxalyl* derivative (V), which is nitrated, the oxalyl group removed by acid hydrolysis, and the amino-group in the resulting 3 : 3′-*dinitro*-4 : 4′-*diaminodiphenylarsinic acid* (VI) subsequently replaced by hydroxyl by alkaline hydrolysis. The usefulness of this method is marred, however, by the fact that at temperatures approaching 140°, oxalic acid causes fission of the molecule of *pp*′-diaminodiphenylarsinic acid to some extent, the product being a mixture from which the pp′-*dioxalylaminodiphenylarsinic acid* can be isolated by means of the sparing solubility of its barium salt in cold dilute ammoniacal solution.



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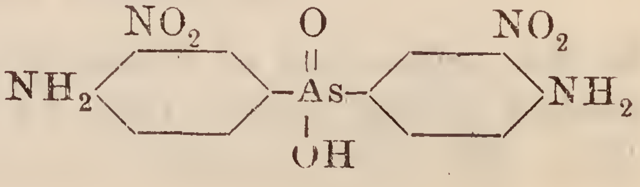
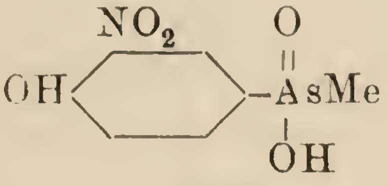
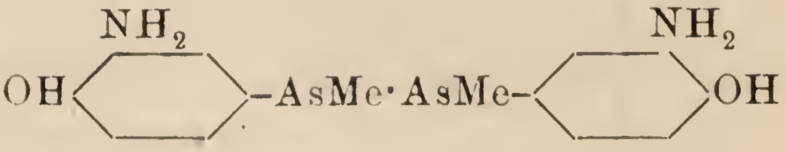


(VI.)

Bertheim (*Ber.*, 1915, **48**, 352), who described the preparation and reduction of 3-nitro-4-hydroxyphenylmethylarsinic acid (VII), found that the direct reduction of the nitro-acid with sodium hyposulphite led to an impure product, whilst if the hyposulphite reduction were stopped at the amino-acid stage and the reduction continued with hypophosphorous acid, 3:3′-diamino-4:4′-dihydroxydiphenyldimethyldiarsine (VIII) was obtained.

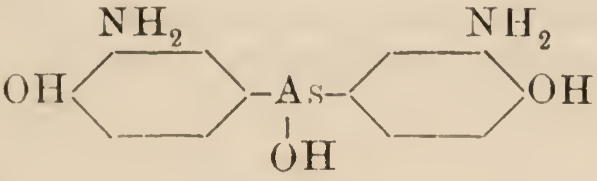


(VII.)

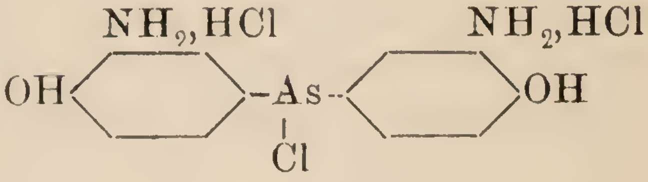


(VIII.)

In the case of 3:3′-dinitro-4:4′-dihydroxydiphenylarsinic acid, complete reduction with sodium hyposulphite leads to 3:3′-*diamino-4:4′-dihydroxydiphenylarsenious hydroxide* (IX), for the crude, sparingly soluble reduction product, dissolved in methyl alcohol containing hydrochloric acid and precipitated with concentrated hydrochloric acid, gives rise to 3:3′-*diamino*-4:4′-*dihydroxydiphenylarsenious chloride dihydrochloride* (X), which was obtained in a crystalline condition.



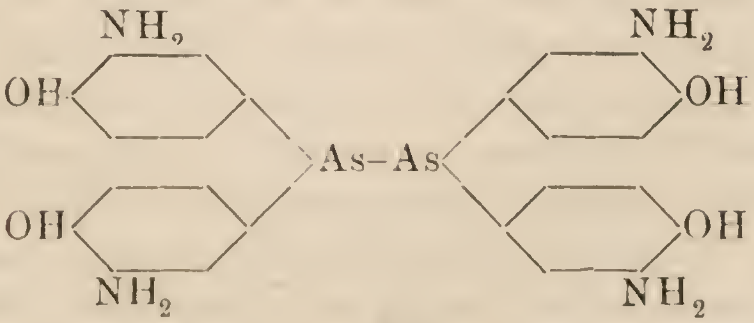
(IX.)



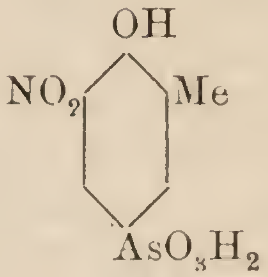
(X.)

If the acid is first reduced to the corresponding *amino-acid* by means of sodium hyposulphite and then completely reduced by means of hypophosphorous acid, 3:3′:3″:3‴-*tetra-amino*-4:4′:4″:4‴-*tetrahydroxytetraphenyldiarsine* (XI) is obtained.

The degree of reduction of the products is readily ascertained by titration with a standard solution of iodine, using starch as indicator, oxidation to the corresponding arsinic acids taking place (compare Gaebel, *Arch. Pharm.*, 1911, **249**, 241).



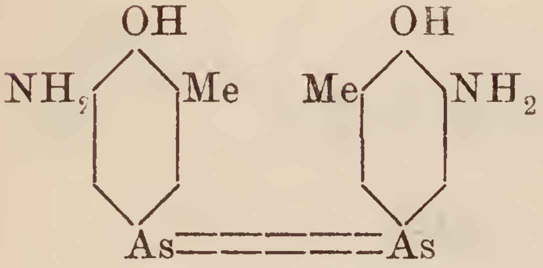
(XI.)



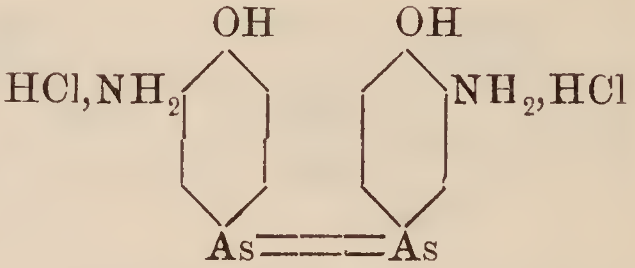
(XII.)

5-Nitro-6-hydroxy-*m*-tolylarsinic acid (XII), first obtained by Benda and Bertheim (*loc. cit.*) by the nitration of 4-hydroxy-*m*-

tolylarsinic acid, can also be prepared from 4-*oxalylamino*-m-*tolylarsinic acid* by the series of reactions outlined above, the preparations from both sources being identical. On reduction with sodium hyposulphite, diaminoarseno-*o*-cresol (4:4′-dihydroxy-5:5′-diamino-3:3′-dimethylarsenobenzene) (XIII) (D.R.-P. 224953) was obtained. This was converted into the *dihydrochloride*, which closely resembles salvarsan (XIV).

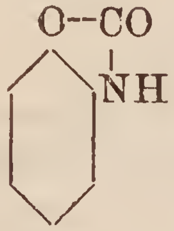


(XIII.)

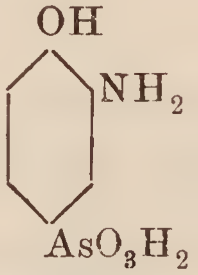


(XIV.)

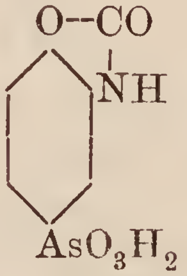
By the action of carbonyl chloride on *o*-aminophenol, 1:2-dihydrobenzoxazolone (XV) is obtained (Schmitt and Henschel, *J. pr. Chem.*, 1888, [ii], **37**, 27; E. von Meyer, *ibid.*, 1915, [ii], **92**, 255). This reaction was applied to 3-amino-4-hydroxyphenylarsinic acid (XVI), giving 1:2-*dihydrobenzoxazolone*-4-*arsinic acid* (XVII), which, on reduction with sodium hyposulphite, yielded the corresponding *arsenobenzene*. It had been hoped that this would prove sufficiently acidic to dissolve in sodium carbonate, but although it dissolves very readily in sodium hydroxide, it is practically insoluble in the carbonate.



(XV.)



(XVI.)



(XVII.)

The estimation of arsenic in organic compounds has been the subject of a recent communication by Ewins (T., 1916, **109**, 1355), who considers that the method devised by Lehmann (*Apoth. Zeit.*, 1912, **27**, 545) for the estimation of arsenic in salvarsan and neosalvarsan, whilst applicable to certain closely allied derivatives, fails entirely in a large number of cases owing to the fact that the preliminary treatment with potassium permanganate and sulphuric acid does not bring about complete oxidation. By a slight alteration of the conditions, it has now been found possible to extend this estimation to a considerable number of substituted phenylarsinic acids containing nitro-, amino-, hydroxy-, methoxy-, bromo-, and other groups, which, by the unmodified method, gave very untrustworthy results owing to incomplete oxidation.

EXPERIMENTAL.

pp′-*Dihydroxydiphenylarsinic Acid* (III).

pp′-Dihydroxydiphenylarsinic acid was obtained by Benda (*Ber.*, 1908, **41**, 2371) by diazotising *pp′*-diaminodiphenylarsinic acid in dilute hydrochloric or sulphuric acid, and decomposing the diazo-derivative by passing steam through the solution. Diazotisation in hydrochloric acid, however, gives a product substituted to some extent by chlorine, whilst in sulphuric acid alone the product is very dark-coloured and difficult to purify.

10·5 Grams of sodium *pp′*-diaminodiphenylarsinate, containing $6H_2O$, were dissolved in 75 c.c. of water, 10 c.c. of sulphuric acid added, and diazotised with 50 c.c. of a normal solution of sodium nitrite. The product was mixed with an equal volume of acetic acid to keep the hydroxy-acid produced in solution, and warmed on the water-bath until the elimination of nitrogen had ceased. After boiling with charcoal, the solution was concentrated under diminished pressure, when, on cooling, rather more than 5 grams of the hydroxy-acid separated, whilst the mother liquors yielded further small quantities, the total yield amounting to 75—80 per cent. of the theoretical. The acid is very sparingly soluble in acetone or chloroform, but readily so in methyl alcohol, ethyl alcohol, or 50 per cent. acetic acid, from which it crystallises in plates melting and decomposing at 259° (corr.). (Found: $C=49{\cdot}0$; $H=3{\cdot}7$; $As=25{\cdot}3$. $C_{12}H_{11}O_4As$ requires $C=49{\cdot}0$; $H=3{\cdot}8$; $As=25{\cdot}5$ per cent.)

3:3′-*Dinitro*-4:4′-*dihydroxydiphenylarsinic Acid* (IV).

6·3 Grams of *pp′*-dihydroxydiphenylarsinic acid were dissolved in 35 c.c. of concentrated sulphuric acid and treated gradually with a mixture of 2·5 c.c. of nitric acid (D 1·44) and 2·5 c.c. of sulphuric acid, the temperature being kept at −5° to −3°. After the mixture had remained in a cool place for some time, it was poured on 250 grams of powdered ice, the precipitated acid being collected and washed with water. The yield amounted to 94 per cent. of the theoretical. The acid is almost insoluble in boiling water, fairly readily soluble in glacial acetic acid, and sparingly so in 50 per cent. acetic acid, from which it separates in minute, rhomboidal prisms melting and decomposing at 230° (corr.).

Found: $C=37{\cdot}5$; $H=2{\cdot}6$; $N=7{\cdot}3$; $As=19{\cdot}6$.

$C_{12}H_9O_8N_2As$ (384·1) requires $C=37{\cdot}5$; $H=2{\cdot}4$; $N=7{\cdot}3$; $As=19{\cdot}5$ per cent.

3 : 3′-*Diamino*-4 : 4′-*dihydroxydiphenylarsenious Chloride Dihydrochloride* (X).

Two grams of the preceding compound, dissolved in 20 c.c. of water and 5·4 c.c. of 2*N*-sodium hydroxide, were added to a solution of 6 grams of magnesium chloride and 24 grams of sodium hyposulphite in 200 c.c. of water. The resulting solution, which immediately decolorised, was heated to 60° in an atmosphere of carbon dioxide for an hour, a further 10 grams of sodium hyposulphite being added after half an hour. The small quantity of grey powder obtained was dissolved in a little methyl alcohol containing hydrochloric acid, filtered, and added to 100 c.c. of concentrated hydrochloric acid, when a crystalline precipitate gradually separated. This was collected, washed with a few drops of glacial acetic acid and a little ether, and dried in a vacuum over sulphuric acid, the yield amounting to 0·5 gram.

The compound forms glistening leaflets readily soluble in water or methyl alcohol, but sparingly so in concentrated hydrochloric acid. On heating, it darkens above 170° and melts at 215° (corr.).

Found: C = 36·2; H = 3·8; N = 6·9; Cl = 27·0.

$C_{12}H_{12}O_2N_2ClAs,2HCl$ (399·5) requires C = 36·0; H = 3·5; N = 7·0; Cl = 26·7 per cent.

0·1000 Gram required 0·061 gram of iodine for complete oxidation, against 0·063 theoretically required.

3 : 3′-*Diamino*-4 : 4′-*dihydroxydiphenylarsinic Acid and* 3 : 3′ : 3″ : 3‴-*Tetra-amino*-4 : 4′ : 4″ : 4‴-*tetrahydroxytetraphenyldiarsine Tetrahydrochloride.*

5·1 Grams of 3 : 3′-dinitro-4 : 4′-dihydroxydiphenylarsinic acid were dissolved in 80 c.c. of water and 24 c.c. of 2*N*-sodium hydroxide. The solution, cooled to 0°, was treated in one operation with 17·6 grams of commercial sodium hyposulphite, the temperature rising to about 30°. When the reaction was complete, the solution was cooled, 20 c.c. of 2*N*-hydrochloric acid were added, and as the acid only partly separated, it was salted out by the addition of sodium chloride, and was obtained as a sandy, crystalline precipitate fairly readily soluble in water or methyl alcohol, but sparingly so in ethyl acetate. The yield amounted to 46 per cent. of the theoretical. (Found: N = 8·5. $C_{12}H_{13}O_4N_2As$ (324·1) requires N = 8·6 per cent.)

Two grams of the acid were heated at 60° for one hour in an atmosphere of carbon dioxide with 20 c.c. of hypophosphorous acid

(D 1·15) and a trace of hydriodic acid. As the colourless base obtained by neutralising a test portion of the resulting solution rapidly became purple on exposure, the remainder was added without neutralisation to 150 c.c. of hydrochloric acid. The white precipitate which gradually separated was collected, washed with a few drops of glacial acetic acid and a little dry ether, and dried in a vacuum. The product is readily soluble in water or methyl alcohol.

Found: N = 7·6; Cl = 19·7.

$C_{24}H_{24}O_4N_4As_2,4HCl$ (728·1) requires N = 7·7; Cl = 19·5 per cent.

0·1001 Gram required 0·103 gram of iodine for complete oxidation, as against 0·104 gram theoretically required.

pp′-*Dioxalylaminodiphenylarsinic Acid* (V).

When oxalic acid is allowed to react with *pp*′-diaminodiphenylarsinic acid at a temperature approaching 160°, some fission of the molecule results, so that a mixture is obtained from which the desired product can be isolated by taking advantage of the sparing solubility of its barium salt in cold dilute ammonia, the barium salt of *p*-aminophenylarsinic acid being precipitated only on boiling.

8·4 Grams of sodium *pp*′-diaminodiphenylarsinate containing $6H_2O$ were intimately mixed with 15·1 grams of oxalic acid and heated in an oil-bath with constant stirring at 140° until most of the water had disappeared, and then to 160° until quite hard. The product was well ground with 80 c.c. of water and 8 c.c. of hydrochloric acid, collected, and well washed with water. It was then dissolved in ammonia and treated with a cold solution of barium chloride. The resulting precipitate was collected, well washed with water, and decomposed by grinding with dilute hydrochloric acid. A small quantity which remained in the acid was precipitated on dilution. pp′-*Dioxalylaminodiphenylarsinic acid* is only sparingly soluble in boiling water, alcohol, or methyl alcohol, and practically insoluble in benzene, ether, or ethyl acetate. It is more readily soluble in acetic acid or 50 per cent. acetic acid, and crystallises in slender needles which contain $4H_2O$.

Found: loss at 110° = 13·8.

$C_{16}H_{13}O_8N_2As,4H_2O$ requires 14·1 per cent.

In material dried at 110°, C = 44·1; H = 3·3; N = 6·4.

$C_{16}H_{13}O_8N_2As$ (436·2) requires C = 44·0; H = 3·0; N = 6·4 per cent.

Nitration with a mixture of nitric and sulphuric acids, and subsequent acid hydrolysis, led to the formation of 3:3′-*dinitro*-4:4′-

diaminodiphenylarsinic acid (VI), a yellow, crystalline powder very sparingly soluble in water and the usual organic solvents.

Found: N = 14·3.

$C_{12}H_{11}O_6N_4As$ (382·1) requires N = 14·7 per cent.

This was converted by warming with an excess of potassium hydroxide solution into 3 : 3′-dinitro-4 : 4′-dihydroxydiphenylarsinic acid, identical with that described above.

6-*Oxalylamino*-m-*tolylarsinic Acid*.

Five grams of sodium 6-amino-*m*-tolylarsinate (containing $3H_2O$) and 6 grams of oxalic acid were intimately mixed and heated first at 140° until most of the water had been driven off, and then at 160° until quite dry. The residue was triturated with 50 c.c. of water and 7 c.c. of hydrochloric acid, collected, and washed with water. The product, which was anhydrous, amounted to rather more than 3 grams. It was found to be sparingly soluble in hot alcohol, ethyl acetate, or acetone, more readily so in hot water, and readily so in 50 per cent. acetic acid, from which it crystallised in elongated, rhombic prisms.

Found: N = 4·5; As = 24·6.

$C_9H_{10}O_6NAs$ (303·1) requires N = 4·6; As = 24·7 per cent.

5-*Nitro*-6-*amino*-m-*tolylarsinic Acid*.

Six grams of the above oxalyl derivative were dissolved in 20 c.c. of sulphuric acid, and a mixture of 1·2 c.c. of nitric acid (D 1·4) and 1·2 c.c. of sulphuric acid was gradually added below 15°. When the reaction was complete, the product was poured into 100 c.c. of water, boiled under a reflux condenser for two hours, cooled, and the acid which separated, amounting to 4·6 grams, collected. 5-*Nitro*-6-*amino*-m-*tolylarsinic acid* is fairly readily soluble in boiling water, from which it separates in slender needles consisting of a mixture of the yellow anhydrous form and the orange hydrated form. It gradually passes completely into the latter, which contains $1\frac{1}{2}H_2O$.

Found: loss at 110° = 9·3.

$C_7H_9O_5N_2As,1\frac{1}{2}H_2O$ requires H_2O = 9·0 per cent.

In dried substance, N = 9·9.

$C_7H_9O_5N_2As$ (276·1) requires N = 10·1 per cent.

5-*Nitro*-6-*hydroxy*-m-*tolylarsinic Acid* (XII).

Two grams of the acid just described were heated on the water-bath with 10 c.c. of 40 per cent. potassium hydroxide solution until a test portion no longer showed the presence of an amino-group. The product was then cooled and acidified with hydrochloric acid, giving almost the theoretical yield of 5-nitro-6-hydroxy-*m*-tolylarsinic acid. This was compared with a specimen prepared by Benda and Bertheim's method (*Ber.*, 1911, **44**, 3445), and found to be identical with it. Both products, when crystallised rapidly from boiling water, formed clusters of slender, yellow needles, and when crystallised slowly from 50 per cent. acetic acid, well-defined, rhombic prisms. When heated in the same bath, both products decomposed explosively at 310°, whilst the mixture of the two behaved identically.

The *acetyl* derivative, prepared by the action of acetic anhydride in the presence of a trace of pyridine, is fairly readily soluble in methyl or ethyl alcohol or boiling water, but sparingly so in cold water or ethyl acetate. When crystallised from water, it forms colourless, spherical nodules, which are anhydrous.

Found: N = 4·4.

$C_9H_{10}O_7NAs$ (319·1) requires N = 4·4 per cent.

4:4′-*Dihydroxy*-5:5′-*diamino*-3:3′-*dimethylarsenobenzene Dihydrochloride.*

The reduction of the 5-nitro-6-hydroxy-*m*-tolylarsinic acid was effected by means of sodium hyposulphite under the conditions described by Ehrlich and Bertheim (*Ber.*, 1912, **45**, 757; compare D.R.-P. 224953). The dihydrochloride, which was obtained in a yield of 70 per cent. of the theoretical, formed a pale yellow, microcrystalline powder readily soluble in water or methyl alcohol, much less readily so in ethyl alcohol, and practically insoluble in ether or acetone.

Found: Cl = 13·6; As = 29·9.

$C_{14}H_{16}O_2N_2As_2,2HCl,2H_2O$ (503·1) requires Cl = 14·1; As = 29·8 per cent.

3-*Amino*-4-*hydroxyphenylarsinic Acid.*

The reduction of nitrohydroxyphenylarsinic acid to the corresponding amino-acid by means of sodium hyposulphite has been described in D.R.-P. 224953. The following modification of the method gives excellent results.

Twenty-six grams of 3-nitro-4-hydroxyphenylarsinic acid were dissolved in 200 c.c. of *N*-sodium hydroxide, cooled to −2°, and to the well-stirred solution 65 grams of sodium hyposulphite (80 per cent.) were added in one operation. The colour of the solution disappeared at once, and the temperature rose to 25°, whilst the amino-acid commenced to deposit. The precipitation was completed by the addition of 23 c.c. of hydrochloric acid (D 1·12). The acid was collected and well washed with water; the yield in several experiments ranged between 65 and 80 per cent. of the theoretical.

1:2-*Dihydrobenzoxazolone*-4-*arsinic Acid* (XVII).

A solution of 11·6 grams of aminohydroxyphenylarsinic acid in 150 c.c. of 5 per cent. sodium hydroxide, cooled by ice and stirred vigorously, was gradually treated with 110 c.c. of a 6·5 per cent. solution of carbonyl chloride in toluene. At the conclusion of the reaction, the two layers were separated, the aqueous layer being extracted with ether and then acidified with hydrochloric acid, when the oxazolone separated as a sandy, crystalline precipitate in a yield amounting to 83 per cent. of the theoretical.

It is sparingly soluble in alcohol, but readily so in boiling water, from which it separates in colourless, prismatic needles which are anhydrous. On heating, it rapidly decomposes above 250° without melting.

Found: C = 32·5; H = 2·5; N = 5·4; As = 28·6.

$C_7H_6O_5NAs$ (259·0) requires C = 32·4; H = 2·3; N = 5·4; As = 28·9 per cent.

1:2:1′:2′-*Tetrahydro*-4-*arsenobenzodioxazolone*.

2·3 Grams of 1:2-dihydrobenzoxazolone-4-arsinic acid were dissolved in a mixture of 50 c.c. of water and 8 c.c. of 2*N*-sodium hydroxide, added to a solution of 15 grams of sodium hyposulphite and 3 grams of magnesium chloride in 70 c.c. of water, and heated, with stirring, for an hour at 60° in an atmosphere of carbon dioxide. A yellow, granular precipitate gradually formed, which, after cooling, was collected and well washed with water. A portion was dried to constant weight in a vacuum over sulphuric acid, and formed a pale yellow, granular powder insoluble in water or the usual organic solvents or in sodium carbonate, but readily soluble in aqueous sodium hydroxide.

Found: N = 6·5; As = 35·6.

$C_{14}H_8O_4N_2As_2$ (418·1) requires N = 6·7; As = 35·9 per cent.

The remainder was dissolved in aqueous sodium hydroxide, and the *sodium* salt precipitated by the addition of alcohol. This, after drying in a vacuum, was obtained as a pale yellow, fairly stable powder readily soluble in water, sparingly so in alcohol, and insoluble in ether.

Estimation of Arsenic in Substituted Phenylarsinic Acids.

For the estimation of arsenic in the foregoing and many other compounds, the following modification of Lehmann's method (*Apoth. Zeit.*, 1912, **27**, 545) has been used, and has been found to give good results generally with substituted phenylarsinic acids.

0·2 Gram of the powdered substance is accurately weighed and intimately mixed in a 250 c.c. flask with 1 gram of potassium permanganate. Five c.c. of 50 per cent. sulphuric acid are added, followed by a further 10 c.c. of concentrated sulphuric acid when the first reaction has ended. After a few minutes, 10 c.c. of water are added, and the mixture is heated for half an hour to gentle boiling, precautions being taken against loss by spraying. The manganese dioxide is then removed by a slight excess of hydrogen peroxide, 30 c.c. of water are added, and the solution is again boiled for ten minutes, after which a dilute solution of potassium permanganate is added drop by drop until a faint, permanent pink tinge is obtained. This is discharged by the addition of a drop of a dilute solution of oxalic acid. The solution is then cooled, 2·5 grams of potassium iodide are added, the whole being allowed to remain for an hour, and the liberated iodine titrated by means of thiosulphate. A blank experiment should be carried out alongside each estimation, and the final reading corrected accordingly.

The following are examples of the results obtained:

	As	
Substance.	Found.	Calc.
3-Nitro-4-hydroxyphenylarsinic acid	28·4, 28·4	28·5
p-Aminophenylarsinic acid	34·5, 34·5	34·6
1 : 2-Dihydrobenzoxazolone-4-arsinic acid	28·6	28·9
3-Nitro-4-aminophenylarsinic acid	28·9, 28·8	28·6
3 : 3′-Dinitro-4 : 4′-dihydroxydiphenylarsinic acid	19·6, 19·5	19·5
p-Bromophenylarsinic acid	26·5	26·7

In conclusion, the author desires to express his thanks to Professor F. L. Pyman for his interest during the course of the investigation.

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